REMARKS

THE AMENDMENT TO THE SPECIFICATION

The amendment to the specification adds the Application Serial Number of the sister application that was filed on the same date as the instant application. No new matter is added to the application with the amendment to the specification.

ANTICIPATION REJECTION - WILTON ET AL.

Claims 1-5, 9, 12-14, and 26 stand rejected under 35 U.S.C. § 102(b) as anticipated by Wilton et al. (HUMAN MUTATION 11:252-258 (1998)). This rejection is traversed.

As recited in claim 1, the present invention is directed to a dual-purpose primer for amplifying a target nucleotide sequence in a target molecule, wherein the target nucleotide sequence contains a site of interest proximal to or contained within a secondary structure forming region that, in the absence of the primer, results in an unwanted secondary structure in an amplicon formed under amplification conditions so as to prevent detection of the site of interest, wherein the primer comprises: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region to prevent formation of the unwanted secondary structure.

Wilton et al. teach the use of a snapback primer for the detection of a single-strand conformation polymorphism ("SSCP). SSCP analysis is a method of detecting genetic mutations that requires no manipulation of PCR products beside gel fractionation. Under the PCR-SSCP method, PCR is followed by SSCP analysis, the latter of which entails the electrophoretic separation of single-stranded nucleic acids. Because single base mutations, i.e., single base changes, may disrupt secondary structure of single-stranded DNA, single base mutations are detected based upon a change in motility of the PCR product through the gel.

One of the limitations of SSCP analysis is that a significant percentage of base changes may not be detected through SSCP because the base changes are in regions that are not involved in the overall secondary or tertiary structure of the single-stranded PCR product. The snapback method overcomes the shortcomings of SSCP analysis. When PCR is carried out with a snapback primer, the PCR products of the snapback primer will have a terminus with the potential for reannealing or "snapping back" to the normal allele, but not the mutant allele. In this manner, the region containing the mutation under investigation is forced into playing a role in the secondary and tertiary structures of the single-stranded PCR products. This feature of the snapback primer is discussed at page 258 of Wilton et al. where it is explained that the mutation under investigation (there, the mdx mutation) was not amenable to SSCP

analysis until a conformation change was engineered into the amplification product. In other words, unlike the primers and probes of the present invention, which are designed to *prevent formation of secondary and tertiary structures*, the snapback primers of Wilton et al. *produce secondary or tertiary structures*.

As is clear from the discussion set forth above, the snapback primer of Wilton et al. is designed to produce a PCR product that retains its secondary or tertiary structure so that the size of the PCR product may be determined by gel electrophoresis. By contrast, the blocking sequence of the claimed invention is designed to disrupt secondary structure so that the site of interest may be identified through means such as flow cytometry. The foregoing analysis shows that the "functional" language from claim 1 identified by the Examiner (Office Action, page 3) is a feature that is necessary to define the invention and in so doing, does in fact impart structural limitations to the claimed dual-purpose primer.

Because the teachings of the Wilton et al. reference do not anticipate the claimed invention, applicants request withdrawal of this rejection.

ANTICIPATION REJECTION - USPN 5,573,906 TO BANNWARTH ET AL.

Claims 1, 2, and 4-7 stand rejected under 35 U.S.C. § 102(b) as anticipated by Bannwarth et al. (USPN 5,573,906). This rejection is traversed.

As indicated in the title of this patent, Bannwarth et al. teach a process of detecting nucleic acids using a hairpin-forming oligonucleotide primer and an energy detection transfer system. The process uses a 5′-labeled primer with a self-complementary sequence in an amplification reaction followed by a detection step using a 3′-labeled probe, which is complementary to a portion of the extended product. Because the primer is self-complementary, it forms a hairpin loop on itself (*see*, col. 3, ll. 47-51); to facilitate the backfolding, the oligonucleotide primer includes a non-nucleotidylic linker group (col. 2, ll. 32-33). The energy-detection system is basically a labeling system (*see*, col. 7, ll. 11-26, 66, and 67) that is facilitated by the close proximity of the two ends of the oligonucleotide as a result of the backfolding of the oligonucleotide (*see*, Figure 1).

The Bannwarth et al. reference make no mention of secondary structure in the target nucleotide and concerns itself only with providing an amplification primer that has a double-stranded section for the purpose of facilitating the labeling process, i.e., the energy transfer process. The primer disclosed in Bannwarth et al. is clearly not a dual-purpose primer that has a sequence complementary to a segment of the target nucleotide sequence within the secondary structure forming region.

Because the teachings of the Bannwarth et al. reference do not anticipate the claimed invention, applicants request withdrawal of this rejection.

ANTICIPATION REJECTION - US PAT PUB 2002/0028455 TO LAIBINIS ET AL.

Claims 1 and 5-8 stand rejected under 35 U.S.C. § 102(b) as anticipated by Laibinis et al. (US Patent Publication No. 2002/0028455). This rejection is traversed.

As indicated in the title of this patent publication, Laibinis et al. teach a method for attaching oligonucleotides to solid supports. At paragraph 0010, it is explained that the surface-bound arrays of the probes described therein are generated by covalently attaching a nucleic acid probe to a surface by hybridizing the nucleic acid probe, which has a pairing sequence and a target moiety, to a capture probe, wherein a covalent bond is formed between the surface (or a surface-bound nucleic acid) and the complementary pairing sequence on the capture probe. Where a PCR primer is used instead of a probe, an oligonucleotide sequence is covalently attached to the PCR primer and a crosslinking moiety is covalently bound to the oligonucleotide sequence, which in turn is covalently bound to the surface (para. 0023; Figure 3).

The only mention of secondary or tertiary structure in the D3 reference is at paragraph 0132 where it is stated that the oligonucleotide target moieties may be RNA, DNA, single-stranded, double-stranded, triple-stranded, linear, or contain elements of secondary or tertiary structure. This single isolated disclosure relating to secondary and tertiary structure clearly indicates that the D3 reference is not viewing secondary structure as a problem and is not intending the oligonucleotides disclosed therein as having a dual purpose of binding to the target and disrupting unwanted secondary structure; thus, even if the Examiner is not giving any weight to the recitation that the blocking sequence prevents formation of the secondary structure, the D3 reference still does not teach or suggest that the primers or probes disclosed therein have a sequence that binds to the target moiety at a site outside the secondary structure and another site within the secondary structures (*see*, claim 1 of the instant application, steps (a) and (b)).

Because the teachings of the Laibinis et al. reference do not anticipate the claimed invention, applicants request withdrawal of this rejection.

ANTICIPATION REJECTION - USPN 6,268,147 TO BEATTIE ET AL.

Claims 1, 17, and 18 stand rejected under 35 U.S.C. § 102(b) as anticipated by Beattie et al. (USPN 6,268,147). This rejection is traversed.

As is clear from the title of the instant application, the purpose of the dual-purpose primer of the claimed invention is to enhance hybridization assays by disruption of secondary structure formation. As recited in claim 1, the dual-purpose primer achieves this purpose by having the following features: (a) a primer sequence complementary to a segment of the target nucleotide sequence other than the secondary

structure forming region; and (b) a blocking sequence substantially complementary to a segment of the secondary structure forming region to prevent formation of the unwanted secondary structure.

Beattie et al. teach tandem hybridization techniques to address various problems associated with nucleic acid hybridizations including the spontaneous formation of secondary structure in the single-stranded target nucleic acid.

The differences between the dual-purpose primers of the present invention and the tandem hybridization technique described in Beattie et al. are most evident when Figures 5 and 10 of the instant application are compared against Figures 13A, 13B, 14A, 14B, 15A, and 15B of Beattie et al.

As shown in Figures 5 and 10 of the instant application, the dual purpose primer of the claimed invention includes three sections: a blocker region (B); a spacer region (S); an optional base (O), which prevents unwanted priming; and a primer region (P), which is the section of the dual purpose primer that initiates the amplification of the target nucleic acid sequence. As is shown in these figures, when the blocker sequence (B) hybridizes internally to the section to be blocked (B′) on the target strand, unwanted secondary structure formation is prevented.

By contrast, as shown in Figures 13A and 13B of Beattie et al., the hybridization technique of Beattie et al. includes hybridization of a molar excess of labeled oligonucleotides *in tandem* to a heat-denatured target strand of a double-stranded target DNA (*see also*, col. 7, l. 66, to col. 8, l. 8). As is shown in Figures 14A and 14B, the probes of Beattie et al. do ***not*** have blocking sequences. Further, as is clear from Figures 13 to 15, as well as the text of Beattie et al., the Beattie et al. probes are intended only to identify the sequence of a target analyte and ***not*** to amplify the target strand.

Because the Beattie et al. reference does not anticipate the claimed invention, applicants request withdrawal of this rejection.

OBVIOUS REJECTION - WILTON ET AL. IN VIEW OF THE STRATEGENE CATALOG

Claims 27-30 stand rejected under 35 U.S.C. § 103(a) as obvious over Wilton et al. in view of the 1998 Stratagene Catalog. This rejection is traversed.

Claims 27-30 are kit claims that depend from claim 1. Wilton et al., the primary reference applied to these claims, is discussed above. The Examiner cites the Strategene Catalog for the motivation to combine the reagents of claim 1 into a kit. Because the teachings of the Wilton et al. reference do not lead the ordinary artisan to the claimed invention, the teachings of a kit from the Stratagene Catalog will not serve to render obvious the invention as recited in claims 27-30.

Because the Examiner's hypothetical combination of Wilton et al. in view of the Strategene Catalog does not render the claimed invention obvious, applicants request withdrawal of this rejection.

OBVIOUS REJECTION - BANNWARTH ET AL. IN VIEW OF THE STRATEGENE CATALOG

Claim 28 stands rejected under 35 U.S.C. § 103(a) as obvious over Bannwarth et al. in view of the Strategene Catalog. This rejection is traversed.

Claim 28 is a kit claim that ultimately depends from claim 1. Bannwarth et al., the primary reference applied to these claims, is discussed above. The Examiner cites the Strategene Catalog for the motivation to combine the reagents of claim 1 into a kit. Because the teachings of the Bannwarth et al. reference do not lead the ordinary artisan to the claimed invention, the teachings of a kit from the Stratagene Catalog will not serve to render obvious the invention as recited in claim 28.

Because the Examiner's hypothetical combination of Bannwarth et al. in view of the Strategene Catalog does not render the claimed invention obvious, applicants request withdrawal of this rejection.

OBVIOUS REJECTION - BEATTIE ET AL. IN VIEW OF THE STRATEGENE CATALOG

Claims 28-34 stands rejected under 35 U.S.C. § 103(a) as obvious over Beattie et al. in view of the Strategene Catalog. This rejection is traversed.

Claims 28 to 31 are kit claims that depends from claim 1. Beattie et al., the primary reference applied to these claims, is discussed above. The Examiner cites the Strategene Catalog for the motivation to combine the reagents of claim 1 into a kit. Because the teachings of the Beattie et al. reference do not lead the ordinary artisan to the claimed invention, the teachings of a kit from the Stratagene Catalog will not serve to render obvious the invention as recited in claims 28-31.

Claims 32-34 are directed to a hybridization probe that has the same elements as claim 1; accordingly, the discussion of Beattie et al. set forth for claim 1 applies with equal force to claims 32-34.

Because the Examiner's hypothetical combination of Beattie et al. in view of the Strategene Catalog does not render the claimed invention obvious, applicants request withdrawal of this rejection.

OBVIOUSNESS REJECTION - WILTON ET AL. IN VIEW OF USPN 6,054,568 TO FISHER ET AL.

Claims 10, 11, 15, and 16 stand rejected under 35 U.S.C. § 103(a) as obvious over Wilton et al. in view of Fisher (USPN 6,054,568). This rejection is traversed.

Claims 10, 11, 15, and 16 depend from claim 1. Wilton et al., the primary reference applied to these claims, is discussed above. The Examiner cites Fisher for the teachings of the non-natural bases iso-cytosine and iso-guanine. Because Wilton et al. does not teach or suggest the invention as recited in claim 1, the additional teachings of Fisher et al. will not serve to render obvious the invention as recited in dependent claims 10, 11, 15, and 16.

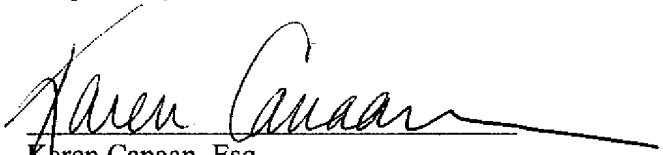
Because the Examiner's hypothetical combination of Beattie et al. in view of Fisher et al. does not render the claimed invention obvious, applicants request withdrawal of this rejection.

CONCLUSION

With this paper, each of the Examiner's rejections have been fully addressed and overcome. Because there will be no outstanding issues for this matter upon entry of this paper, applicants respectfully request withdrawal of all claim rejections and passage of this application to issue.

Any questions regarding this paper or the application in general may be addressed to the undersigned attorney at 650-251-7713 or kcanaan@mintz.com.

Respectfully submitted,

By: 

Karen Canaan, Esq.
Registration No. 42,382
MINTZ LEVIN
1400 Page Mill Road
Palo Alto, CA 94304

TRA 2190351v.1